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Familial atrial septal defect in a single generation

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A family is presented in which 5 of 6 children have secundum atrial septal defects without involvement of any other generations. Of the 5 affected children, 2 had additional cardiac malformations (mild pulmonary stenosis and a ventricular septal defect). No environmental or pharmacological aetiology was implicated.

This paper describes a family in which 5 of 6 children have atrial septal defects of the secundum type proven by cardiac catheterization. Two of the sibs have undergone corrective operations. While the familial aspects of secundum atrial septal defects have been previously documented (Bizarro *et al.*, 1970; Howitt, 1961; Johansson and Sievers, 1967; Nora, McNamara, and Fraser, 1967; Williamson, 1969; Zetterqvist, 1960; Zuckerman *et al.*, 1962), this is believed to be the largest single affected generation to be recorded. This family also differs from other case reports in that all other generations are unaffected.

Case reports

The parents are 39 and 38 years, Both have had recent physical examinations, including chest *x*-rays and electrocardiograms, which show no evidence of heart disease. Except for one nephew in the father's family with rheumatic heart disease, there is no history of heart disease in either family.

The product of the first pregnancy was full term and weighed 4082 g at birth but died at 3 days of age due to 'brain damage'. The next two pregnancies terminated in spontaneous abortions at 10 weeks and 12 weeks' gestation, respectively.

Case 1 Robert (13 years) is the product of the 4th pregnancy which was complicated by considerable vomiting without maternal ingestion of medication. He was admitted to Milwaukee Children's Hospital at the age of 10 years for evaluation of an asymptomatic murmur. Physical examination revealed a widely split second heart sound with an ejection murmur at the left sternal border and no diastolic murmur. Electrocardiogram revealed a QRS frontal axis of 100° and incomplete right bundle-branch block. The chest *x*-ray was within normal limits. Cardiac catheterization findings were consistent with an atrial septal defect (ASD). The left-to-right shunt was 1·3 l./min per m^2 and the pulmonary/systemic flow ratio (Q_p/Q_s) was 1·4/1. He remains asymptomatic.

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Case 2 Chris (12 years) was the full-term product of a normal pregnancy and uncomplicated delivery. At age 7 years he was admitted to hospital because of episodes of nocturnal dyspnoea. The physical examination revealed a widely split and fixed second heart sound, an ejection murmur at the left sternal border, and a short early diastolic rumble. The electrocardiogram showed right axis deviation. The chest *x*-ray revealed cardiomegaly, a prominent pulmonary artery, and increased pulmonary vascularity. At cardiac catheterization an atrial septal defect was found with a left-to-right shunt of 3·0 l./min per m^2 and a Q_p/Q_s of 1·9/1. The child had an operation under cardiopulmonary bypass at age 8 years, and is now doing well.

Case 3 Kim (11 years) has had a negative physical examination. Electrocardiogram and chest *x*-ray were within normal limits. A recent dye dilution curve suggested a left-to-right shunt. For this reason catheterization was performed using oximetry, dye dilution, and cineangiography, all of which showed no evidence of atrial septal defect or any other heart disease.

Case 4 Karen (10 years) underwent physical examination at 3 years of age because of her family's history of heart disease. At that time a fixed and widely split second heart sound and an ejection murmur were noted. The electrocardiogram revealed right axis deviation, right ventricular hypertrophy, and incomplete right bundle-branch block. Cardiac catheterization findings were consistent with a moderate atrial septal defect. The left-to-right shunt was 4·6 l./min per m^2 and the $Q_p/Q_s = 2·5/1$. At age $3\frac{1}{2}$ years she had a corrective operation and is now doing well.

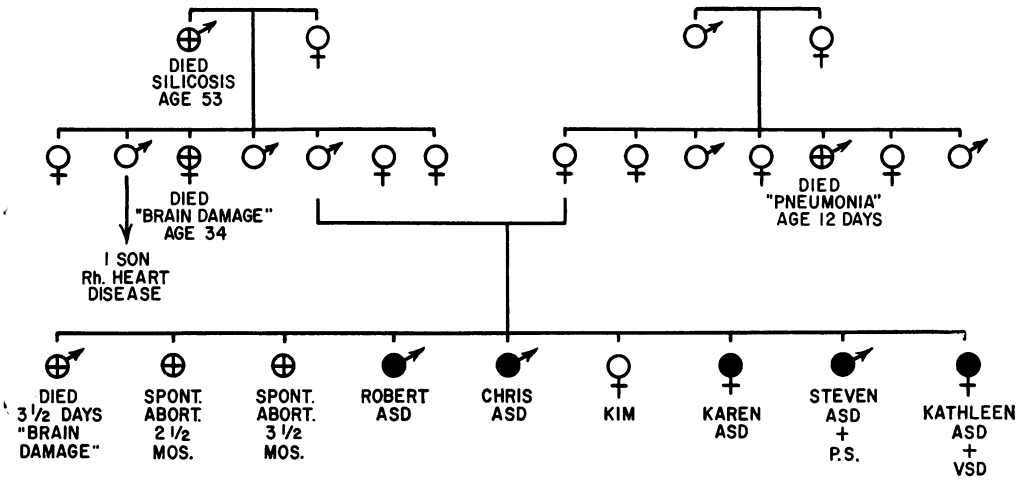

FIG. *Family pedigree.* ○, *alive and well;* ⊕, *dead;* ●, *alive with congenital heart disease.*

Case 5 Steven (9 years) was evaluated at age 5 for a murmur heard 2 years previously. On physical examination the second heart sound was widely split and fixed, and a loud ejection murmur was present at the left upper sternal border. Right axis deviation, right ventricular hypertrophy, and incomplete right bundle-branch block were present on the electrocardiogram. Chest *x*-ray showed right ventricular enlargement and increased pulmonary vascularity. At cardiac catheterization an atrial septal defect was present with a left-to-right shunt of 2·9 l./min per m^2 and a $Q_p/Q_s = 2/1$. In addition there was a 30 mmHg gradient across the pulmonary valve. Because he had an episode of subacute bacterial endocarditis, he has not yet had a corrective operation.

Case 6 Kathleen (8 years) was noted to have increased pulmonary vascularity at 3½ years on a chest *x*-ray taken for suspected pneumonia. Cardiac evaluation at 4 years of age revealed a fixed and widely split second heart sound, a systolic thrill along the left sternal border, and a mid-diastolic rumble in the same area. The electrocardiogram revealed right ventricular hypertrophy and incomplete right bundle-branch block. The chest *x*-ray showed mild cardiomegaly and increased pulmonary vascularity. Cardiac catheterization revealed the presence of *both* an atrial septal defect and a ventricular septal defect. Total left-to-right shunt was 4·1 l./min per m^2 with a $Q_p/Q_s = 3/1$. On follow-up examinations, the pansystolic murmur disappeared, as did the thrill, and it is believed that the ventricular septal defect has closed spontaneously. Dye dilution studies still show the presence of a left-to-right shunt, presumably through the atrial opening.

Discussion

The familial incidence of secundum atrial septal defect has been well documented (Bizarro *et al.*, 1970; Howitt, 1961; Johansson and Sievers, 1967; Nora *et al.*, 1967; Williamson, 1969; Zetterqvist, 1960; Zuckerman *et al.*, 1962). Williamson (1969) reported 4 cases in 2 generations. Zuckerman *et al.* (1962) listed 8 cases in 4 generations of a single family. Zetterqvist (1960) described a family in which 13 cases (8 proven and 5 suspected)

TABLE I *Catheterization results in sibs with atrial septal defect*

Name	*Age at catheterization (yr)*	*Per cent O_2 saturation*					*Pressure (mmHg)*			*L–R shunt (l./min per m^2)*	Q_p/Q_s
		SVC	*RA*	*RV*	*PA*	*FA*	*RV*	*PA*	*FA*		
Robert	10	70	80	81	81	96	26/3/5	24/10	113/68	1·3	1·44
Chris*	7	71	82	84	82	99	23/0/5	21/7	122/56	3·0	1·90
Karen*	4	54	76	76	78	91	40/0/8	31/7	121/53	4·6	2·50
Steven†	5	76	81	83	83	95	47/0/3	17/7	107/59	2·9	2·00
Kathleen‡	4/12	47	70	77	77	97	37/5	35/12	106/57	4·0	3·00

* Patients operated upon.
† Atrial septal defect and pulmonary stenosis.
‡ Atrial and ventricular septal defect.

TABLE 2 *PR intervals*

Name	*Heart rate per min*	*PR interval (sec)*
Robert	82	0·16
Chris	108	0·13
Karen	110	0·16
Steven	75	0·13
Kathleen	115	0·13

existed in 4 generations. Howitt (1961) showed the presence of an atrial septal defect in a mother, her daughter, and one of the two grandchildren. Johansson and Sievers (1967) found a family with 6 proven and one probable atrial septal defect in 3 generations.

In our family of 6 sibs, 5 have atrial septal defects. We believe that our report constitutes the largest single generation with the greatest proportion of proven atrial septal defects (5/6).

In contradistinction to the usual situation with atrial septal defect in which numerous generations are affected (Campbell and Polani, 1961), our group has had no affected relatives (Fig.). Nora *et al.* (1967) and Williamson (1969) believe that the risk of atrial septal defect in a child is related to the total number of relatives with the lesion. Certainly, the incidence of congenital heart disease in sibs can rise sixfold in those families where a previous sib has had a congenital heart defect (McKeown, MacMahon, and Parsons, 1953).

The fact that the mother had two spontaneous abortions is interesting in that Williamson (1969) found no differences in the number of spontaneous abortions in families with atrial septal defects when compared to the general population. It is also unlikely that the first child died because of an atrial septal defect, since Campbell (1970) recently stated that the mortality rate of atrial septal defect in the first decade was 0·7 per cent per annum, and that no significant mortality appeared until the third decade.

Additional malformations were found in 2 of our subjects: ventricular septal defects and pulmonary stenosis. In their study of 170 patients with atrial septal defect, Campbell and Polani (1961) found that 16 per cent had additional cardiac malformations and over 5 per cent had pulmonary stenosis.

Genetic factors have long been suspected of playing a part in the aetiology of atrial septal defect. Autosomal dominant (Bizarro *et al.*, 1970; Howitt, 1961; Johansson and Sievers, 1967; Zetterqvist, 1960; Zuckerman *et al.*, 1962), autosomal recessive (Yao *et al.*, 1968), and some dominant and some recessive (Campbell and Polani, 1961) have been suggested to explain familial patterns. Bizarro *et al.* (1970) described a syndrome of atrial septal defect with prolonged AV conduction and attributed its aetiology to a single mutant autosomal dominant gene. There was no prolongation of atrioventricular conduction in the electrocardiograms of any member of our family (Table 2).

References

Bizarro, R. O., Callahan, J. A., Feldt, R. H., Kurkland, L. T., Gordon, H., and Brandenburg, R. O. (1970). Familial atrial septal defect with prolonged atrioventricular conduction. A syndrome showing the autosomal dominant pattern of inheritance. *Circulation*, **41**, 677.

Campbell, M. (1970). Natural history of atrial septal defect. *British Heart Journal*, **32**, 820.

Campbell, M., and Polani, P. E. (1961). Factors in the aetiology of atrial septal defect. *British Heart Journal*, **23**, 477.

Howitt, G. (1961). Atrial septal defect in three generations. *British Heart Journal*, **23**, 494.

Johansson, B. W., and Sievers, J. (1967). Inheritance of atrial septal defect. *Lancet*, **1**, 1224.

McKeown, T., MacMahon, B., and Parsons, C. G. (1953). The familial incidence of congenital malformations of the heart. *British Heart Journal*, **15**, 273.

Nora, J. J., McNamara, D. G., and Fraser, F. C. (1967). Hereditary factors in atrial septal defect. *Circulation*, **35**, 448.

Williamson, E. M. (1969). A family study of atrial septal defect. *Journal of Medical Genetics*, **6**, 255.

Yao, J. K. Y., Thompson, M. W., Trusler, G. A., and Trimble, A. S. (1968). Familial atrial septal defect of the primum type. A report of four cases in one sibship. *Canadian Medical Association Journal*, **98**, 218.

Zetterqvist, P. (1960). Multiple occurrence of atrial septal defect in a family. *Acta Paediatrica (Uppsala)*, **49**, 741.

Zuckerman, H. S., Zuckerman, G. H., Mammen, R. E., and Wassermil, M. (1962). Atrial septal defect. Familial occurrence in four generations of one family. *American Journal of Cardiology*, **9**, 515.

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